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TOXIC JAUNDICE AND ANTI-SYPHILITIC TREATMENT*

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THE subject on which I am asked to speak, namely, jaundice, is one in which I have been interested for a great many years. In 1919 I delivered the Lettsomian lectures on jaundice, and last year, at the Royal College of Physicians, the Lumelian lectures on the same subject. In endeavouring to understand the relationship of toxic jaundice to anti-syphilitic treatment, one does not want to have a narrow idea of what drugs will cause jaundice, because if one's outlook is very limited one will not really know how to handle cases and arrange treatment. A grasp of the whole subject of jaundice and what it means is therefore necessary.

Jaundice so far as concerns the life of the patient is not of significance; it is the liver function that matters, and that is why I want to deal with the subject rather from its broad aspects.

Jaundice was defined by Osler as a condition characterised by coloration of the skin and mucous membrane and fluids of the body by the bile pigments. That definition would be rather amplified and made more precise at the present day. Blood contains a certain percentage of bilirubin; if that percentage rises to a certain figure it means that there is latent jaundice, and if it rises beyond that figure there is manifest jaundice. The modern physician would perhaps define jaundice as a condition in which the Van den Bergh reaction shows a figure of above half a unit, half a unit being the normal amount. There is another quantitative test where the colour of the blood serum is matched—this is known as the icterus index test. Normally, the blood serum has a colour corresponding to from 1 to 5 units; when the figure rises to from 5 to 15, it means latent jaundice, and above 15, manifest jaundice. These tests are nowadays very

* Based on an Address delivered before the Medical Society for the Study of Venereal Diseases, April 8, 1932.

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commonly applied to patients who are being treated for syphilis, and one can recognise when there is danger. If the Van den Bergh reaction or the icterus index shows that latent jaundice is present it means that there is danger, and that treatment must be suspended for a time. These tests, therefore, are not just abstruse scientific tests, but are of great practical value.

As regards the classification of jaundice, the English classification divides it into the obstructive, the toxic and the hæmolytic type. I think that is by far the best classification. To-night I am dealing with toxic jaundice and not with the other two categories.

The liver has a variety of functions, and it is well to realise this before one talks about toxic jaundice and anti-syphilitic treatment. One function of the liver is the production of bile. In such production red blood cells are broken down by the cells of Kupfer lining the capillaries, and the bile pigment is produced and is carried through the liver cell to the bile canniculi, and so collected into the bile duct. The liver cell determines what kind of reaction one gets by the Van den Bergh test. In toxic jaundice the bile does not normally go through the liver cell into the little capillaries at the centre of the lobule ; the liver cell is damaged, and it cannot change the bile as it should do, so that one does not get quite a normal bile. In toxic jaundice also the liver cell swells and the bile cannot get through the proper channel, so that there is a certain amount of obstruction. That is the reason why the Van den Bergh tests now in these cases of toxic jaundice are very inconclusive. In the old procedure it was said that obstructive jaundice gave the direct test and toxic and hæmolytic jaundice the indirect test, but we know nowadays that toxic jaundice is partly obstructive and partly toxic. The liver swells up, and the bile cannot get through the capillaries and so is dammed back. In these cases, therefore, there is a biphasic reaction. In America it is called the direct reaction. But, at any rate, in toxic jaundice one does not get the kind of test which was expected when Van den Bergh first published his work.

I have said that jaundice does not matter as regards the life of the patient. People can have their bile ducts completely blocked and live for a long time, a year or more, with very little trouble, except perhaps for itching

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of the skin, and so on. In toxic jaundice the danger is in the accompanying degeneration of the liver cells, which gives rise to serious symptoms owing to the absence of liver function.

The liver has among other functions that of fat metabolism, the storing up of fat in the cells. Curiously enough, in these cases of toxic jaundice the liver cells are loaded with fat, but the fat is not the same kind as that of the healthy liver cell. It is composed of saturated fatty acids, whereas in the healthy liver cell the fat globules are composed of unsaturated fatty acids.

The liver has also the function of glycogen storage. That is an important practical point in the treatment of venereal diseases, because one knows that the liver cell which has a lot of glycogen in it is a very resistant cell and can stand a certain amount of poison. We are all aware that the drinking of alcohol on an empty stomach has a much more potent effect than the drinking of it after a good dinner, and the custom of taking dessert and port wine has a certain amount of scientific basis; one has the glucose in the blood, and that is stored in the liver as glycogen, so that a person can enjoy his glass of port wine without coming to any harm. Glycogen function, therefore, is an important function of the liver. Most physicians who are treating cases for syphilis and giving the powerful remedies, take care that their patients have amounts of glucose in some form or other within a few hours of the injection of salvarsan or bismuth, or whatever it may be. One finds that the patients are much more tolerant in such cases. It is never wise to give any of these powerful toxic remedies to a patient who is debilitated and dyspeptic and not eating well. There is a great risk of getting liver damage with these toxic changes.

Another important function of the liver cell—perhaps the most important—is to deal with the protein metabolism in the body. This is the key of the situation. If the liver cells stop functioning we have at once that wonderful picture of the clinical symptoms of acute yellow atrophy, or icterus gravis, or hypo-hepatism, if one likes to use that term. The liver cells stop working, and death occurs in two or three days. Death occurs because the liver cell, which had regulated the protein metabolism, had gone out of action, and we get the accumula-

tion of all these toxic products of protein. If the liver stops working the body gets flooded with these poisons, protein decomposition molecules, and death occurs from a condition very like uræmia. That is why when we have some poison, say, salvarsan or bismuth, which is causing jaundice, it is not the jaundice that matters, save in so far as it means that the liver cells are damaged in function, and with the bile-producing function damaged there is some danger to the protein metabolism function.

The liver has another very important function. I think I am responsible for its name—I used it in 1922 in one of the British Medical Association discussions, namely, the toxiphylactic function. If any poison gets into the body, the liver filters it out and prevents it from poisoning the heart and brain and so on. The liver is really the great protector against poisons. The liver does it work very well ; it fights to the death. If there is poison in the body, the liver will go on absorbing until its cells are killed. That is the reason why, when persons are given salvarsan or bismuth or any of these powerful drugs which are used in the treatment of syphilis, the liver will protect against an overdose.

Just a word about the tests for liver function. There are a number of these—the lipase test, the fibrinogen test, and so forth, but the only test that is used to any extent in this country is the lævulose or galactose test. The patient is given 30 grammes of lævulose or galactose, and if his liver is functioning normally there is very little rise in the blood sugar. If the liver is failing in function, there is an up-and-down movement which indicates impairment of function, and in these cases of jaundice due to anti-syphilitic remedies this test will furnish a marked positive reaction.

I think one can consider the liver damage in toxic jaundice by recalling what happens to the liver histologically. The cell will be damaged, and it may undergo swelling, fatty degeneration, or necrosis. Fibrous tissue may develop between the cells and the state of fibrosis may be progressive. Often after the administration of substances like the arsenic compounds which act on the liver there is some necrosis of the liver cells. These disappear and are replaced by fibrous tissue, and one may have a progressive fibrosis going on for years. I have

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had two or three cases where patients died ten years after having toxic jaundice from some poison—trinitrotoluene, tetrachlorethane, and salvarsan.

The liver is not an organ that takes things lying down. If it is damaged the cells may die, but it has the property of regenerating its cells, and new liver cells are formed. The liver can regenerate its cells, but what it cannot regenerate is its architecture, its portal canals, and so on. The old "topers" who drink alcohol to great excess damage their liver, and new cells are produced by the liver, but the architecture of the liver is not corrected, and so they have ascites, and so forth. The liver is a tough organ, but if it is damaged its architecture suffers and the patient may show the symptoms of cirrhosis.

The present days are perilous ones from the pharmacological point of view. The market is being flooded with all sorts of organic compounds, such as atophan, quinophane, new anæsthetics with fancy names so that the ordinary doctor has not the faintest notion what they contain, avertin, and many others, and nearly all these things are liver poisons. In addition to being liver poisons, they are kidney poisons, so that while one may get an excellent anæsthetic which delights the surgeon, the physician in charge of the case may suffer grave anxiety, as I have done only to-day in treating a case of suppression of urine with a certain amount of toxic jaundice due to one of these new anæsthetics. I beg of you all to realise when using these powerful drugs that you are dealing with two-edged weapons and should go warily. These drugs should not be given unless the patient is in a fit condition to stand them, and it should also be remembered that it takes three weeks for a dose of salvarsan to be excreted. If doses are given in a shorter period than three weeks, a certain amount of accumulation will occur, and it is important to bear that in mind.

As regards the drugs that act on the liver, causing toxic jaundice, there are several important points to be remembered. The drugs are very elusive in their action, and it is well to have a wide knowledge of the possibilities when giving these drugs. If you have the knowledge, you will be able to ward off the dangers. The drugs vary very much in their intensity of action. We are only dealing with anti-syphilitic remedies to-night,

but these vary also in their action on the liver. For example, salvarsan and the arsenobenzol derivatives have a powerful action on the liver, while bismuth and mercury are less toxic. The kind of drug used, therefore, is important. Another very important point is idiosyncrasy. Certain patients are extraordinarily sensitive to a particular drug. There are patients who cannot tolerate salvarsan. A few years ago I saw an officer, aged thirty-two. He had had jaundice in 1915 during the war. In May, 1928, he contracted syphilis. On June 27th of the same year 0.3 gramme of NAB was given, and on July 2nd, 0.45 gramme. On July 7th he developed jaundice. On July 27th, twenty days after the jaundice had developed, 0.1 gramme NAB was given intravenously, and he thereupon developed a very severe attack of toxic jaundice lasting three weeks, and one dare not give him any more arsenic. He was treated with mercury and also with bismuth injections. Neither of these had a toxic action on the liver in this case, and he got quite well, though there was some difficulty in getting his Wassermann reaction negative.

Another important point is what I sometimes call symbiosis. If a person has one disease and then gets another disease on the top of it, one has an entirely different picture from what might be expected from mere arithmetical addition. One gets a sort of geometrical progression. That is a thing important to bear in mind when treating patients with these anti-syphilitic remedies. If they have influenza or a cold or any infection, and are given these anti-syphilitic liver poisons, a very powerful and dangerous effect may be produced, as to which one cannot be too careful. A patient may lose his life through a little lack of care in that respect. I beg you, therefore, to remember the importance of symbiosis—the combination of action of two diseases or effects—in dealing with these cases. I have notes of one interesting case as showing how careful one ought to be. It was a man aged forty-five, who gave a history of syphilis, and the Wassermann reaction was plus. Between April 4th, 1920, and June 22nd he had twelve injections of 0.6 gramme of salvarsan. On January 1st, 1928, he began a further course of injections, with 0.3 gramme, and on January 14th and 28th, and February 11th and March 9th he had 0.6 gramme. He thus had a course of sal-

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varsan allowing good intervals—a fortnight—between each dose. But on February 15th, in the interval between the last two doses he had twelve teeth removed under chloroform anæsthesia, the operation lasting nearly two hours. On March 9th, in the evening, after the last injection of salvarsan, his temperature rose to 105° and severe vomiting occurred. On March 10th he went to business and fainted three times. On March 11th he was sick and jaundice developed. On March 12th the jaundice was deeper, the temperature was 99.5 , and the urine contained a trace of albumen and a trace of acetone. That patient died on March 17th with symptoms of hypohepatitis or acute yellow atrophy. He had had doses of salvarsan, but while taking that treatment he had chloroform. He was a busy man and did not want to waste time, and so he underwent the dental operation in the middle of the salvarsan course. What could you expect? He died of toxic jaundice. If he had not had that chloroform and his teeth out in the middle of the salvarsan course, he would probably not have got the jaundice. Another case, which I have seen only to-day, is that of a man who had an ulcer on his tongue. Streptococci were found and it looked like a streptococcal ulcer. This happened four or five weeks ago. There were some red spots on the body, which gave an indication of what really was the matter. This was a primary chancre. The patient was given anti-streptococcic serum, and it did him good and made the ulcer a little better, but he was given a dose of NAB, 0.4 gramme, just after his reaction from the anti-streptococcic serum. He got a very high temperature, was acutely ill, had a rash all over, and a thorough stirring up. He would not have had such a reaction if he had not had the anti-streptococcic serum. That again is an instance of symbiosis, of two processes acting together. His Wassermann reaction, which was negative, became most violently positive after he had his dose of 0.4 gramme NAB. The NAB had produced a powerful toxic effect. He has had two doses since, and no reaction whatever from the NAB. With the first dose there was a serum reaction intensifying his condition to a much greater extent than would be indicated by the mere sum of the two complaints.

Another interesting point with regard to these liver poisons is what I call the time factor. A dose of salvarsan

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may knock the liver out. I have seen that happen many times. In other words, the patient has died really of toxic jaundice before the jaundice has had time to develop. No doubt, the jaundice could have been found if sought for by the usual tests, but there was no manifest jaundice at the time of death. Fortunately this does not happen so often to-day, because the salvarsan compounds are so much more carefully prepared than they used to be and are not nearly so toxic.

Again, a person who has had one or two or more doses of salvarsan may develop toxic jaundice a few weeks afterwards, but he may also develop it several months afterwards, or even a year after the last dose. I have seen it develop as long as a year after salvarsan, and with some of the liver poisons toxic jaundice may occur eighteen months after the last administration. These liver poisons set up a fibrosis in the liver which is progressive. I have records here of three cases where death has occurred from liver damage after the original poisoning.

On giving a dose of salvarsan the patient may suffer a little giddiness, but, as a rule, there is very little effect. A few hours afterwards there may be a slight rise of temperature, perhaps $\frac{1}{2}^{\circ}$ or 1° , a little nausea, sickness, slight diarrhoea, the next morning a trace of albumen, and after that the patient is all right. That is the kind of thing which commonly happens. But sometimes the jaundice develops, and then there will be observed the colour, the tendency to nausea and sickness, and some discomfort in the abdomen, because the toxic jaundice is due to the action of poison on the liver, and the liver cells are swollen, with consequent discomfort. The patient usually is alarmed by the jaundice and goes to bed and is treated, very little else in the way of symptoms occurring if things go well. But one may have the development of hypo-hepatism or sometimes accompanying necrosis of the liver. The liver cells may cease to function and die, in which case the growth of the toxic symptoms of what used to be called acute yellow atrophy takes place. Mental disturbance occurs, irritability, a little sickness, twitching, restlessness, possibly some air hunger, then some delirium, Cheyne-Stokes breathing, hæmorrhages in the gums or elsewhere, all this being followed by a comatose condition, with a rise of tempera-

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ture to 106° or 107° , and then death occurs. During the last forty-eight hours the urine will contain albumen and casts and possibly blood. That is the sort of picture, lasting about seventy-two hours. When a person who has had salvarsan is sick or is a little quarrelsome I always begin to suspect some such reaction. If the cases are treated very promptly the result may be warded off. The treatment is simple—rest, fruit juice and glucose, and plenty of alkalis, such as bicarbonate of soda, citrate of soda, citrate of potash, and Vichy water. If the patient cannot take them by the mouth, glucose (5%) should be given by the rectum or subcutaneously or intravenously.

Theoretically, insulin ought to be helpful in these cases, but it does not do always to use what is theoretically indicated. Insulin is very good, of course, in diabetic coma, but my experience is that it is dangerous to use in these cases of acute yellow atrophy. I mention that because I have heard people say that the thing to do in these cases is to give insulin. I have done it, and my answer is, "Don't." You should pursue your treatment as energetically as possible; you have about twelve hours in which to prevent the result I have just indicated.

During the war I wrote about tetrachlorethane poisoning, and the *British Medical Journal* asked me to write a paper on the treatment of toxic jaundice. At that time I did not think the treatment was much good, but I did write an article on it, in which I recommended alkalis. I did not lay so much stress on glucose as I should have done, because not so much was known about glucose at that time. But I had many letters afterwards from practitioners who said they had followed out my treatment and had had marvellous recoveries. They had had more marvellous recoveries than I had had myself. It is possible in these cases of threatening toxic jaundice to ward it off, but if the comatose stage is reached I have rarely seen a case recover.

Prophylactic treatment is very important. I have already mentioned glucose before injection. Care should be taken that the patient is fit, also that a dose of salvarsan is not being given when the remains of the last dose are already present. Some people in the venereal diseases clinics give doses every week, but not the full maximum dose. Something like 0.4 or 0.6 gramme of NAB can be given every week, but one cannot go on

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indefinitely doing that, because by the fifth or sixth week there is a dangerous accumulation.

Toxic jaundice is due to a variety of causes. It is due to numerous chemical poisons of various kinds. It may also arise from bacterial poisons and from protozoal poisons. We must not forget that syphilis itself can cause jaundice. You may when you give a small dose of salvarsan in the early stages of syphilis find jaundice develop, not as a result of salvarsan poisoning, but owing to the liberation of the spirochætal poison.

A word or two about the different remedies which give rise to jaundice. The important drugs which cause toxic jaundice are the arsenic compounds. It was not realised until lately that jaundice was a fairly common symptom in arsenical poisoning. I looked up some of the old cases, and in nearly every one you will find the yellow skin mentioned in the case of the person poisoned by arsenic. But, of course, you get toxic jaundice very commonly from any of the organic derivatives of arsenic, and especially the salvarsan group, and, as I have mentioned, it is very variable in the rapidity of its onset and in the intensity of its action. It is really the liver cell which dominates the situation. Jaundice is the striking symptom because of the colour it produces, but it is not the vital symptom, not a symptom that is going to cause the death of the patient. Mercury used in the form of metal, or calomel, or the perchloride of mercury is not a particularly powerful liver poison, it is more likely to cause suppression of urine, or ulcerative colitis of a very fatal type, and it may cause a very severe stomatitis, but occasionally jaundice may follow mercury. Antimony used to be employed in the treatment of syphilis. This is a liver poison almost as powerful as arsenic. The inorganic bismuth may be taken in quantity by the mouth without any harm resulting, because it is insoluble, except the nitrate of bismuth, which is decomposed into nitrate, and so may give nitrite poisoning. For the treatment of syphilis bismuth is usually given by injection, either intramuscular or subcutaneous. It may cause some gastro-enteritis, and it may cause colitis, and again it may cause jaundice, but that is not a very common symptom. Skin eruption, exfoliated dermatitis and hæmaturia may also follow. But, as a rule, the bismuth does not seem to do much harm. I have, how-

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ever, met with two cases, in one of which very severe nerve symptoms were caused, the patient becoming unconscious and having convulsions, and in the other after a bismuth injection the patient had an acute attack of angina pectoris and died in my arms. Therefore, although bismuth is fairly safe to give, it should not be used recklessly.

Just a word about acriflavine, which used to figure in the treatment of venereal diseases, especially gonorrhœa. If taken by the mouth in tablets or given intravenously, this will cause latent jaundice in quite a large percentage of cases, or even apparent or toxic jaundice.

In conclusion I would advise caution in the use of anti-syphylitic remedies. To be potent they must be used in full therapeutic doses bordering on the toxic dose. Be careful that the liver is not damaged in their administration, for this is the most important risk from the toxicological point of view.

(At the close of his address Sir William Willcox showed through the lantern a number of sections indicating liver changes following various poisons.)